TABLE 1 Change in Lipid and Lipoproteins and Atheroma Progression

	Tertile 1	Tertile 2	Tertile 3	p Value	p Value Adjusting for Treatment Group
LDL-C	0.44 ± 0.24	0.14 ± 0.24	0.32 ± 0.24	0.71	0.69
HDL-C	0.64 ± 0.24	0.43 ± 0.24	−0.22 ± 0.24	0.01	0.10
Triglyceride	−0.03 ± 0.24	0.35 ± 0.24	0.59 ± 0.24	0.07	0.19
Total LDL particles	0.04 ± 0.24	0.35 ± 0.24	0.39 ± 0.24	0.32	0.97
Mean LDL particle size	0.82 ± 0.24	0.51 ± 0.24	−0.54 ± 0.24	<0.001	0.003
Large LDL	0.65 ± 0.24	0.16 ± 0.24	−0.04 ± 0.24	0.047	0.25
Small LDL	−0.35 ± 0.24	0.44 ± 0.24	0.70 ± 0.24	0.002	0.07

Values are mean ± SD. Changes in percent atheroma volume were stratified according to tertiles of percentage change in lipid and lipoprotein parameters.
C = cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

not surprising because of the established cardiovascular risk in this setting.

Insulin resistance, hyperglycemia, hypertriglyceridemia, and systemic inflammation promote small LDL particle accumulation in diabetes. Even after controlling for the favorable effects of pioglitazone on these factors, increasing LDL particle size was associated with less disease progression. This has important implications for the development of diabetic therapies and the increased use of lipid-lowering agents to more effectively lower cardiovascular risk.

Preethi Mani, MD
Kiyoko Uno, MD, PhD
Julie St. John, MS
Stuart Kupfer, MD
Alfonso Perez, MD
E. Murat Tuzcu, MD
Stanley L. Hazen, MD, PhD
Steven E. Nissen, MD
***Stephen J. Nicholls, MBBS, PhD**

*South Australian Health and Medical Research Institute
P.O. Box 11060
Adelaide, SA, 5001
Australia
E-mail: Stephen.nicholls@sahmri.com

http://dx.doi.org/10.1016/j.jacc.2015.05.023

Please note: Dr. Nissen has received research support to perform clinical trials through the Cleveland Clinic Coordinating Center for Clinical Research from Pfizer, AstraZeneca, Novartis, Roche, Daiichi-Sankyo, Takeda, Sanofi, Resverlogix, and Eli Lilly; and is a consultant/advisor for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. Dr. Nicholls has received speaking honoraria from AstraZeneca, Pfizer, Merck Schering-Plough, and Takeda; consulting fees from AstraZeneca, Pfizer, Merck Schering-Plough, CSL Behring, Boehringer Ingelheim, Takeda, Roche, NovoNordisk, LipoScience, Amgen, Omthera, Reseverlogix, and Anthera; and has received research support from AstraZeneca, Eli Lilly, Amgen, Takeda, Roche, Novartis, Anthera, Resverlogix, and Lipid Sciences. Drs. Perez and Kupfer are employees of Takeda Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Nicholls SJ, Tuzcu EM, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol 2008;52:255–62.

2. Nicholls SJ, Tuzcu EM, Wolski K, et al. Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: insights from the PERISCOPE study. J Am Coll Cardiol 2011;57:153–9.

3. Mora S, Otvos JD, Rosenson RS, et al. Lipoprotein particle size and concentration by nuclear magnetic resonance and incident type 2 diabetes in women. Diabetes 2010;59:1153–60.

4. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol 2002;90:89–94.

Interpreting Blood Pressure in Younger Adults

The remarkable paper from the Chicago Heart Association Detection Project in Industry Study (1) studied cardiovascular mortality (3,119 deaths) over 31 years in 27,081 initially well persons, according to initial categorizations of systolic and diastolic hypertension, isolated diastolic hypertension, isolated systolic hypertension (ISH), high-normal blood pressure (BP), and optimal-normal BP. The results validate recent concerns that results of treating elderly persons (>60 years) cannot be applied universally to younger persons, as in the 18- to 49-year age group described here (2).

The Central Illustration in Yano et al. (1) shows, for male subjects, little or no deviation in outcome up to 20 years compared with high-normal BP or optimal-normal BP, but considerable deviation from the other 2 hypertensive groups. We have argued that ISH in young male subjects may be “spurious”

(3) if based solely on the brachial cuff measurement of systolic pressure without taking into account the shape of the pressure waveform in central and peripheral (i.e., brachial and/ or radial) arteries. We have pressed this view (4) on the European Society of Hypertension/European Society of Cardiology committee (Yano et al. [1] reference 6) on the basis that elevated brachial and radial systolic pressure in young persons (especially tall male subjects) is caused by an exaggerated narrow systolic pressure peak of the radial and brachial pressure waves but a normal aortic pulse. This contrasts with elevated systolic pressure (i.e., ISH) in persons over age 60 years who almost invariably have a much broader systolic peak, which is similar in the aorta and upper limb arteries (Yano et al. [1] reference 41).

On the basis of outcomes in the Chicago study, one would find it hard to justify a randomized study of therapy compared with placebo in ISH of adult male subjects <50 years of age. Another important factor in guidelines, addressed by a cardiology fellow in the same issue of the journal (5) is "patient preference." For the trivial difference in outcome at 20 years, would not most male subjects wish to defer the stigma of disease, the expense, the inconvenience, and side effects of treatment for another year or 2 until issues are clarified? How are young fellows (5) expected to include opinions, guidelines, and patient preference in their discussions with patients <50 years of age with ISH?

*Michael F. O'Rourke, MD DSc
Audrey Adji, Mb MBiomedE
Mayooran Namasivayam, MBBS(Hons), BSc(Med)Hons
*Suite 810, St. Vincent's Clinic
438 Victoria Street
Darlinghurst, Sydney
NSW 2010
Australia
E-mail: m.orourke@unsw.edu.au

http://dx.doi.org/10.1016/j.jacc.2015.04.070

Please note: Dr. O'Rourke is a founding director of both AtCor Medical P/L and Aortic Wrap P/L. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. J Am Coll Cardiol 2015;65:327–35.

2. Peterson ED, Gaziano JM, Greenland P. Recommendations for treating hypertension: what are the right goals and purposes? JAMA 2014;311:474–6.

3. O'Rourke MF, Vlachopoulos C, Graham RM. Spurious systolic hypertension in youth. Vasc Med 2000;5:141–5.

4. O'Rourke MF, Adji A. Guidelines on guidelines: focus on isolated systolic hypertension in youth. J Hypertens 2013;31:649–54.

5. Gosain P. Navigating patient preference and guidelines as a fellow. J Am Coll Cardiol 2015;65:398–9.

REPLY: Interpreting Blood Pressure in Young Adults

We thank Dr. O'Rourke and colleagues for their interest in our findings. Their comments are primarily focused on how our findings can be translated into practice or policy. We urge caution when extrapolating epidemiological findings to clinical recommendations. Research findings, especially those from observational studies, need to be interpreted within the context of global evidence. Unfortunately, evidence is sparse pertaining to long-term outcomes in younger adults with isolated systolic hypertension (ISH). Considering the limited prognostic data on ISH at younger ages, which our data begin to address, we agree with the comment that it would be premature and difficult to conduct randomized intervention trials in a population of younger individuals who would be at low risk for events in the near term. We suggest that the next major step is to replicate our results in other studies with long-term follow-up of younger adults (1,2).

The letter also addresses precision (personalized) medicine. Execution of precision medicine in younger adults with ISH will (partly) resolve concerns regarding patient preference, unnecessary expense, and adverse effects associated with treatments (3). ISH in younger adults appears to be a heterogeneous condition; some have higher stroke volume, whereas others have higher aortic stiffness, or both (4). One size does not seem to fit all in the clinical management of ISH at younger ages. The optimal means to identify higher-risk groups among younger ISH patients merits further research. Clinical characteristics (e.g., body weight, diabetes), biomarkers (e.g., brain natriuretic peptide), and out-of-office blood pressure measurement (e.g., home or ambulatory monitoring) may serve to identify higher-risk individuals. Rather than treating ISH in younger adults as a monolithic disease and continuing to debate whether it is "pseudo" or "spurious" hypertension, detailed phenotyping of ISH patients based on (patho) physiology and global context of risk for cardiovascular events would seem to be most useful to assess an individual patient's expected net benefit from therapy.

Yuichiro Yano, MD, PhD
Stanley S. Franklin, MD
Philip Greenland, MD
*Donald Lloyd-Jones, MD, ScM